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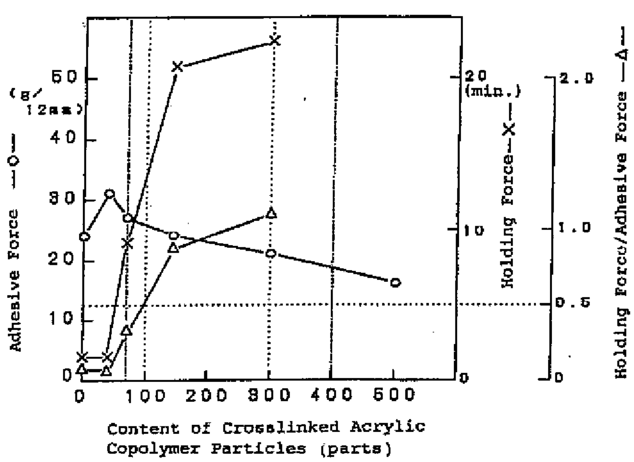
(54) Buprenorphine percutaneous absorption preparation

(57) Disclosed is a buprenorphine percutaneous absorption preparation comprising a backing having formed on one side thereof a pressure-sensitive adhesive layer containing at least one of buprenorphine and a salt thereof, wherein the pressure-sensitive adhesive layer contains an acrylic copolymer and crosslinked acrylic copolymer particles. The buprenorphine percutaneous absorption preparation has excellent pressure-sensitive adhesive characteristics and exerts excellent percutaneous absorption property.

Fig. 1



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Description

FIELD OF THE INVENTION

The present invention relates to a buprenorphine percutaneous absorption preparation and a production method thereof. Particularly, it relates to a buprenorphine percutaneous absorption preparation which is adhered to the skin to effect continuous administration of buprenorphine from the skin into the living body, and to a production method thereof.

BACKGROUND OF THE INVENTION

Buprenorphine and/or a salt thereof is a non-narcotic analgesic which has an analgesic efficacy about 30 times higher than that of morphine and 75 times higher than that of pentazocine and is broadly used in order to relieve cancerous pain and postoperative pain and to assist narcotic drugs. Since buprenorphine and/or a salt thereof sometimes generates side effects such as nausea, emesis, respiratory depression and the like, its use requires the greatest care. In consequence, great concern has been directed toward the development of a dosage form which, when buprenorphine and/or a salt thereof is administered, can prevent too much increase in the blood drug level and control dosage of the drug.

On the other hand, percutaneous administration, which has been vigorously studied recently, has a number of advantages. For example, (1) it is expected that the percutaneous administration achieves a drug effect lasting for 24 hours or longer, which makes such frequent administration unnecessary as required in the cases of injections, sublingual tablets and suppositories, (2) it is expected that the percutaneous administration makes absorption uniform and thus excessive administration can be avoided, and side effects therefore can be relieved, (3) the percutaneous administration neither causes any unevenness in the absorption/retention in the digestive tracts nor experiences first pass effect in the liver and (4) the percutaneous administration is applicable even to a patient whom oral administration is impossible.

However, buprenorphine and/or a salt thereof is extremely poor in percutaneous absorption and thus can be hardly absorbed from the skin in a required dose at a practically available adhesion area, i.e., 100 cm^2 or less.

In consequence, many attempts have been made to develop a percutaneous absorption preparation of buprenorphine and/or a salt thereof which has many advantages as described above (for example, see JP-A-2-191214, JP-A-3-163014, JP-A-3-193732, JP-A-4-217926 and U.S. Patent 5,069,909; the term "JP-A" as used herein means an "unexamined published Japanese patent application").

However, most of these preparations appear to have difficulty in formation thereof or cause adhesive residue and not to be usable in practice, since the skin penetration of a drug is discussed in the form of a solution or a percutaneous penetration enhancer is merely added to a pressure-sensitive adhesive without any special idea. Furthermore, as the percutaneous penetration enhancer contained in these preparations comprises an organic acid, there are some problems from the viewpoint of safety such as generation of skin irritation.

When a percutaneous penetration enhancer is added in order to improve the percutaneous absorption of buprenorphine and/or a salt thereof, the percutaneous penetration enhancer sometimes oozes out to the surface of a plaster during storage, thus changing the properties of the preparation. Further, the addition of a plasticizer or a percutaneous penetration enhancer to the pressure-sensitive adhesive causes a decrease in the cohesive force and, as a result, adhesive residue is formed or stringiness is generated when the preparation is adhered to the skin.

As means for resolving these problems, various methods have been proposed, such as a method in which fine powder silica is added to a pressure-sensitive adhesive (JP-A-2-295565; the term "JP-A" as used herein means an "unexamined published Japanese patent application") or a method in which pressure-sensitive adhesive characteristics are controlled by making an ointment base into gel form through crosslinking of a pressure-sensitive adhesive (JP-A-3-220120).

However, the method in which fine powder silica is added cannot improve pressure-sensitive adhesive characteristics in some cases depending on the formulation composition and formulation method of pressure-sensitive adhesives. Particularly, when a polar substance such as polyethylene glycol is added in a large amount as a percutaneous penetration enhancer, decrease in the viscosity of pressure-sensitive adhesives cannot be prevented.

On the other hand, the method in which entire portion of a pressure-sensitive adhesive is crosslinked by external crosslinking to make it into gel form is markedly excellent in view of the point that the pressure-sensitive adhesive characteristics can be controlled even when a percutaneous penetration enhancer and other additives are used in a large amount.

This method, however, also cannot be used in the case where the percutaneous absorption preparation contains a substance having a crosslinking inhibition action, because the pressure-sensitive adhesive cannot fully be crosslinked. In particular, when a generally and frequently used polyfunctional isocyanate is used as a crosslinking agent, addition of a drug or additive having a hydroxyl group, an amino group, a carboxyl group or a mercapto group to the pressure-

sensitive adhesive causes crosslinking inhibition. For the reason, the drugs and additives having these functional groups cannot be used.

In addition, techniques in which a percutaneous absorption preparation is produced by making a pressure-sensitive adhesive into granular form are disclosed, e.g., in JP-B-58-12255 (the term "JP-B" as used herein means an "examined Japanese patent publication") and JP-B-58-23367, but these techniques have a difficulty in obtaining appropriate pressure-sensitive adhesive characteristics in the case where a percutaneous penetration enhancer and other additives are used in a large amount.

SUMMARY OF THE INVENTION

In view of the above, the inventors of the present invention have conducted intensive studies, with the aim of developing a skin adhesion type percutaneous absorption preparation which has excellent pressure-sensitive adhesive characteristics, does not generate skin irritation and exerts excellent percutaneous absorption, and found that the aforementioned problems can be resolved by blending a pressure-sensitive adhesive with crosslinked acrylic copolymer particles prepared by crosslinking and pulverizing an acrylic copolymer. The present invention has been accomplished on the basis of this finding.

According to the present invention, there is provided a buprenorphine percutaneous absorption preparation comprising a backing having formed on one side thereof a pressure-sensitive adhesive layer containing at least one of buprenorphine and a salt thereof (inclusively referred to as "buprenorphine" sometimes), wherein the pressure-sensitive adhesive layer comprises a first acrylic copolymer and crosslinked acrylic copolymer particles contained therein, which are obtained by crosslinking and pulverization of a second acrylic copolymer. The first acrylic copolymer and second acrylic polymer may be the same or different.

Furthermore, according to the present invention, there is provided a method for producing a percutaneous absorption preparation comprising a backing having formed on one side thereof a pressure-sensitive adhesive layer containing at least one of buprenorphine and a salt thereof, which comprises:

adding a crosslinking agent to a solution of an acrylic copolymer to effect crosslinking,
subjecting the resulting solution to pulverization to prepare a pressure-sensitive adhesive solution containing an acrylic copolymer and crosslinked acrylic copolymer particles,
adding at least one buprenorphine and a salt thereof and optionally a percutaneous penetration enhancer and other additives to the pressure-sensitive adhesive solution, and
coating the backing with the resulting pressure-sensitive adhesive solution to form a pressure-sensitive adhesive layer.

Other objects and advantages of the present invention will be made apparent as the description progresses.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a graph showing relationship between the content ratio of cross-linked acrylic copolymer particles and the physical properties of each percutaneous absorption preparation.

Fig. 2 is a graph showing relationship between the amount of a crosslinking agent added to an acrylic copolymer and the gel percentage of a pressure-sensitive adhesive solution containing cross-linked acrylic copolymer particles.

DETAILED DESCRIPTION OF THE INVENTION

The content of the crosslinked acrylic copolymer particles contained in the pressure-sensitive adhesive layer is generally from 70 to 400 parts by weight per 100 parts by weight of the acrylic copolymer.

It is desirable that the backing to be used in the present invention is made of such a material that a buprenorphine and a percutaneous penetration enhancer contained in the pressure-sensitive adhesive layer do not pass through the backing and escape from its back side surface to cause reduction of the contents. Examples thereof include a single film such as of polyester, nylon, Saran (available from Dow Chem), polyethylene, polypropylene, polyvinyl chloride, ethylene-vinyl acetate copolymer, polytetrafluoroethylene, Surlyn (available from Du Pont), and a metal foil or a laminate film thereof.

Also, in order to improve adhesive force (anchor force) between the backing and a pressure-sensitive adhesive layer which will be described later, it is desirable to make the backing into a laminate film of a non-porous film made of the aforementioned material with woven or non-woven fabric. In that case, it is preferred that the laminate film has a thickness of from 10 to 200 μm.

Alternatively, when characteristics as a single film are desired, it is desirable to subject a single film as the backing

to a so-called undercoat treatment. In that case, it is preferred that the single film has a thickness of from 1 to 100 μm.

The conventional acrylic pressure-sensitive adhesives can be used as the acrylic copolymer to be used in the present invention. The acrylic copolymer generally has a number average molecular weight of 10,000 to 300,000. The amount of the acrylic copolymer to be contained in the pressure-sensitive adhesive layer is generally from 4 to 50 % by weight, preferably from 5 to 35 % by weight based on the weight of the pressure-sensitive adhesive layer.

The acrylic copolymer to be used in the pressure-sensitive adhesive layer of the present invention can be obtained, for example, by using a (meth)acrylic acid alkyl ester, which is commonly used in acrylic pressure-sensitive adhesives, as the main monomer component and copolymerizing it with a functional monomer.

Examples of the (meth)acrylic acid alkyl ester include (meth)acrylic acid alkyl esters having straight or branched-chain C_{4-13} alkyl groups such as butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl and tridecyl, and one or two or more (meth)acrylic acid alkyl esters can be used.

In addition, the (meth)acrylic acid alkyl ester is not particularly limited to the above examples, and a (meth)acrylic acid alkyl ester having a straight or branched-chain alkyl group of 1 to 3 carbon atoms or a (meth)acrylic acid alkyl ester having a straight or branched-chain alkyl group of 14 or more carbon atoms may be used in combination with a (meth)acrylic acid alkyl ester having a straight or branched-chain alkyl group of 4 to 13 carbon atoms.

Examples of the functional monomer copolymerizable with these (meth)acrylic acid alkyl esters include polar monomers and vinyl monomers.

Examples of the copolymerizable polar monomer include a carboxyl group-containing monomer such as (meth)acrylic acid, itaconic acid, maleic acid, maleic anhydride and crotonic acid, a sulfoxyl group-containing monomer such as styrenesulfonic acid, allylsulfonic acid, sulfopropyl (meth)acrylate, (meth)acryloyloxynaphthalenesulfonic acid, and acrylamidemethylpropanesulfonic acid, a hydroxy group-containing monomer such as (meth)acrylic acid hydroxyethyl ester and (meth)acrylic acid hydroxypropyl ester an amido group-containing monomer such as (meth)acrylamide, dimethyl(meth)acrylamide, N-butylacrylamide, N-methylol(meth)acrylamide, and N-methylolpropane(meth)acrylamide, an alkylaminoalkyl group-containing monomer such as (meth)acrylic acid aminoethyl ester, (meth)acrylic acid dimethylaminoethyl ester and (meth)acrylic acid tert-butylaminoethyl ester, a (meth)acrylic acid alkoxyalkyl ester such as (meth)acrylic acid methoxyethyl ester and (meth)acrylic acid ethoxyethyl ester, an alkoxy group (or oxide bonding to side chain)-containing (meth)acrylic acid ester such as (meth)acrylic acid tetrahydrofurfuryl ester, (meth)acrylic acid methoxyethylene glycol ester, (meth)acrylic acid methoxydiethylene glycol ester and (meth)acrylic acid methoxypolyethylene glycol ester, and (meth)acrylonitrile. These monomers may be used alone or as a mixture of two or more to effect copolymerization.

Examples of the vinyl monomer include a vinyl ester such as vinyl acetate and vinyl propionate, and a vinyl monomer having a nitrogen atom-containing hetero ring such as N-vinyl-2-pyrrolidone, methylvinylpyrrolidone, vinylpyridine, vinylpiperidone, vinylpyrimidine, vinylpiperazine, vinylpyrazine, vinylpyrrole, vinylimidazole, vinylcaprolactam and vinyloxazole. These monomers may also be used alone or as a mixture of two or more to effect copolymerization.

One kind or two or more kinds of the polar monomers and vinyl monomers can be copolymerized with the (meth)acrylic acid alkyl ester, but it is desirable to use a carboxyl group-containing monomer, a hydroxy group-containing monomer, an amido group-containing monomer, a (meth)acrylic acid alkoxyalkyl ester or an alkoxy group (or oxide bonding to side chain)-containing (meth)acrylic ester as the copolymerization component in the polymerization, because they have functional groups which become crosslinking points at the time of the crosslinking treatment and can improve cohesive force by increasing glass transition temperature of the acrylic copolymer. In addition, when the improvement of cohesive force and drug solubility is taken into consideration, it is desirable to use vinyl esters or vinyl monomers having a nitrogen atom-containing hetero ring in the copolymerization.

The amount of these copolymerizable polar monomers and/or vinyl monomers to be used in the copolymerization can be arbitrarily set to adjust cohesive force of the acrylic copolymer-based pressure-sensitive adhesive layer or solubility of a drug when included, but it is generally 50% by weight or less, preferably from 2 to 40% by weight.

The acrylic copolymer can be synthesized according known methods, for example, referring to "Kobunshi Jikkengaku Kouza 10 (High Molecules Experimentation Course 10)", edited by The Society of Polymer Science, Japan and published by Kyouritsu Shuppan K.K., Polymerization and Depolymerization Reaction, 1.3. Solution Polymerization (p.13), ii) Polymerization in a Three-Necked Flask.

The crosslinked acrylic copolymer particles take roles in preventing outflow of the percutaneous penetration enhancer which will be described later, imparting cohesive force to the pressure-sensitive adhesive layer, preventing stringiness, and imparting shape-keeping property to the pressure-sensitive adhesive layer. They also take a role in controlling release characteristics of the drug contained.

As the acrylic copolymer to be used in preparing the crosslinked acrylic copolymer particles, the same aforementioned acrylic copolymer as that to be contained in the pressure-sensitive adhesive layer can be used.

The crosslinking reaction for the preparation of the crosslinked acrylic copolymer particles can be effected by carrying out a physical crosslinking treatment in which irradiation with radiation such as ultraviolet rays or electron beam is effected or a chemical crosslinking treatment in which a crosslinking agent such as a polyfunctional compound (e.g., a

polyfunctional isocyanate, an organic peroxide, an organic metal salt, a metal alcoholate, a metal chelate compound, a divinyl compound, an epoxy compound and melamine) is used.

From the point of view of reactivity, workability and the like, it is desirable to carry out a chemical crosslinking treatment using a trifunctional isocyanate, a metal alcoholate comprised of titanium or aluminum or a metal chelate compound. The amount of the crosslinking agent which can be used in the chemical crosslinking reaction is preferably from 0.01 to 2.0 parts by weight based on 100 parts by weight of the acrylic copolymer. In addition, when these crosslinking agents are used, it is desirable to use (meth)acrylic acid as the functional monomer in view of the crosslinking reactivity.

In a production method of the cross linked acrylic copolymer particles, the aforementioned acrylic copolymer and the aforementioned crosslinking agent are uniformly stirred in an appropriate solvent such as an organic solvent, and the mixture is stored as such at a temperature of 50 to 80°C until it is solidified by crosslinking into a gel form, or an acrylic copolymer solution to which a crosslinking agent is added is made into a film using a coating machine which is commonly used in the production of pressure-sensitive adhesive tapes, and the film is subjected to heat aging to effect crosslinking solidification.

The crosslinked and solidified acrylic copolymer composition is pulverized using a pulverizer to obtain crosslinked acrylic copolymer particles. Simultaneously with or prior to the pulverization, the crosslinked and solidified acrylic copolymer composition is diluted to a desired concentration by adding an appropriate solvent. Useful examples of the pulverizer include Gorator (trade name, manufactured by Nittetsu Mining Co., Ltd.), Disintegrator (trade name, manufactured by Komatsu Zenoah Co.), T.K. Cutruder (trade name, manufactured by Tokushu Kika Kogyo Co., Ltd.). In addition to these pulverizers, emulsifying or dispersing apparatuses such as TK Homomixer (trade name, manufactured by Tokushu Kika Kogyo K.K.) and the like can also be used. Of these, it is desirable to use Gorator, Disintegrator or T.K. Cutruder from the viewpoint of the treatment capacity. After pulverization is effected using one pulverizer such as Gorator, if necessary, subsequent pulverization may be effected using the other pulverizer such as a homomixer.

The particle size of the crosslinked acrylic copolymer particles varies depending on the dilution solvent. For example, in the case where the concentration of the crosslinked particles is adjusted to 1% by weight using ethyl acetate as a solvent, the size of the particles swelled with the solvent is preferably controlled to from 0.5 to 50 μm, more preferably from 1 to 20 μm. If the particle size is smaller than 0.5 μm, there is a possibility that no adding effects of the crosslinked particles are exhibited and reduction of cohesive force of the pressure-sensitive adhesive layer and generation of stringiness are caused. If it is larger than 50 μm, there is a possibility of deteriorating coating property to the backing, thereby resulting in streaked coating, irregular coat film surface, uneven thickness and poor appearance of the coat film after drying.

The thus-obtained crosslinked acrylic copolymer particles may be collected by an appropriate method and mixed with other acrylic copolymer solution.

The crosslinked acrylic copolymer particles may be contained in the pressure-sensitive adhesive layer in an amount of generally from 70 to 400 parts by weight, preferably from 100 to 300 parts by weight, based on 100 parts by weight of the acrylic copolymer. If the amount thereof is smaller than 70 parts by weight, there is a possibility that no significant adding effects of the crosslinked particles are exhibited and reduction of cohesive force and generation of stringiness are caused. If it is larger than 400 parts by weight, reduced adhesive force of the pressure-sensitive adhesive layer, poor adhesion to the skin surface and reduced anchor force between the layer and the backing may be caused. It is preferred that the crosslinked particles have a particle size of 0.05 to 20 μm, more preferably from 0.1 to 10 μm in the pressure-sensitive adhesive layer. Such a particle size may be determined taking into account the swelling ratio of the crosslinked particles swelled with a solvent.

Also, as described above, a state in which the crosslinked acrylic copolymer particles are contained in an acrylic copolymer solution can be made by adding the crosslinking agent to an acrylic copolymer solution, applying a crosslinking treatment to a part of the acrylic copolymer and then pulverizing the resulting product. The obtained solution having such a state as such can be used in forming a pressure-sensitive adhesive layer. The continuous process from the acrylic copolymer preparation can provide a pressure-sensitive adhesive layer containing crosslinked acrylic copolymer particles and is convenient since the production steps are simplified.

In this case, the crosslinking percentage (gel percentage) at the time of the completion of the crosslinking reaction is equal to the content of the cross linked acrylic copolymer particles of the pressure-sensitive adhesive layer. Accordingly, the preferred content ratio described above can be obtained by adjusting the amount of the crosslinking agent or the time of the crosslinking reaction and thereby controlling the gel percentage of the acrylic copolymer. For instance, in the case where the gel percentage is controlled to 50 to 60% by weight, the remaining unreacted acrylic copolymer becomes 40 to 50% by weight. Thus, the desired content ratio can be achieved easily.

The pressure-sensitive adhesive layer of the buprenorphine percutaneous absorption preparation of the present invention can contain various additives which include not only buprenorphine but also percutaneous penetration enhancers and other additives such as antioxidants. It is desirable to add these additives in the acrylic copolymer solution containing crosslinked acrylic copolymer particles.

As the percutaneous penetration enhancer, various compounds can be used, which include a compound that has

a function to improve solubility and dispersibility of drugs in the pressure-sensitive adhesive layer, a compound that has a function to improve percutaneous absorption by improving keratin moisture holding ability, keratin softening ability or keratin permeability (loosening), by acting as a permeation enhancer or pore opening agent or by changing surface conditions of the skin and a compound that has these functions simultaneously, and a compound which is possessed of not only these functions but a drug effect improving function to further increase efficacy of drugs.

These percutaneous penetration enhancers are exemplified below:

glycols such as diethylene glycol, propylene glycol, and polyethylene glycol as a compound which mainly improves drug solubility;
oils and fats such as olive oil, squalene and lanolin as a compound which mainly improves drug dispersibility;
urea derivatives such as urea and allantoin as a compound which mainly improves moisture holding ability of keratin;
polar solvents such as dimethyldecyl phosphoxide, methyloctylsulfoxide, dimethyllaurylamide, dodecylpyrrolidone, isosorbitol, dimethylacetamide, dimethyl sulfoxide and dimethylformamide as a compound which mainly improves keratin permeability;
salicylic acid which mainly improves keratin softening ability;
amino acids mainly as a permeability enhancer;
benzyl nicotinate mainly as a pore opening agent;
sodium lauryl sulfate mainly having a function to change surface conditions of the skin; and
salocolum which is jointly used with a drug having excellent percutaneous absorption.

Also useful are a plasticizer such as diisopropyl adipate, phthalic acid esters and diethyl sebacate, hydrocarbons such as liquid paraffin, various emulsifiers, ethoxidized stearyl alcohol, glycerol monoesters such as oleic acid monoglyceride, caprylic acid monoglyceride and lauric acid monoglyceride, higher fatty acid esters such as glycerol diesters, glycerol triesters or a mixture thereof, isopropyl myristate and octyl palmitate, and higher fatty acids such as oleic acid and caprylic acid.

These percutaneous penetration enhancers may be used as a mixture of two or more, and the combination of isopropyl myristate with caprylic acid monoglyceride is particularly preferred as the percutaneous penetration enhancer. The percutaneous penetration enhancer is used in a total amount of preferably from 150 to 400 parts by weight, more preferably from 200 to 300 parts by weight, based on 100 parts by weight of the acrylic copolymer. If the amount thereof is smaller than 150 parts by weight, there is a possibility that no sufficient effect as the percutaneous penetration enhancer may be obtained, and if it is larger than 400 parts by weight, stringiness and adhesive residue due to plasticization of the pressure-sensitive adhesive layer may be caused. Also, the addition in an unnecessarily large amount does not bear proportionally increased effect as a percutaneous penetration enhancer in most cases and is not desirable from the economical point of view.

Also, it is desirable that these percutaneous penetration enhancers have good compatibility with the acrylic copolymer and crosslinked acrylic copolymer particles, because their compatibility with these percutaneous penetration enhancers renders possible addition of a soft feeling to the resulting preparation, improvement of its adhesion and percutaneous absorption and reduction of skin irritation.

As the buprenorphine to be used in the buprenorphine percutaneous absorption preparation of the present invention, not only free buprenorphine but also its various inorganic acid salts such as hydrochloride, sulfate, phosphate and the like or its various organic acid salts such as maleate, succinate, mesylate, tosylate and the like can be used. Of these, it is desirable to use buprenorphine hydrochloride from the viewpoint of practical use.

Also, the amount of buprenorphine to be contained in the pressure-sensitive layer can be determined arbitrarily depending on the kinds of their free. types or salts and the purpose of administration, but is preferably in an amount of from 1 to 60% by weight, more preferably from 5 to 30% by weight. If the amount thereof is smaller than 1% by weight, there is a possibility of exhibiting no sufficient release of the drug necessary for the therapeutic or preventive purpose, and if it is larger than 60% by weight, there is a possibility that the addition exhibits no proportionally greater effect and results in economical disadvantage, and in some cases, adhesive property to the skin is reduced. In the present invention, it is not necessary to dissolve the entire amount of buprenorphine added in the pressure-sensitive adhesive layer, and the drug may be incorporated in an excess amount exceeding the solubility in the pressure-sensitive adhesive layer, so that part of the drug is dispersed in the layer at undissolved state.

The present invention is an effective means particularly in the case where a crosslinking inhibitor is present in the pressure-sensitive adhesive layer. In the prior art percutaneous absorption preparations, optimum pressure-sensitive adhesive characteristics are obtained by making the pressure-sensitive adhesive layer into so-called gel state through crosslinking of the entire portion of the adhesive layer using chemical crosslinking agent such as a trifunctional isocyanate, a metal alcoholate comprised of titanium or aluminum or a metal chelate compound. However, in the case where a crosslinking inhibitor is present in the pressure-sensitive adhesive layer, the crosslinking reaction is inhibited and suf-

ficient pressure-sensitive adhesive characteristics cannot be obtained. Even in such a case, the present invention can provide optimum pressure-sensitive adhesive characteristics by incorporating the crosslinked acrylic copolymer particles in the pressure-sensitive adhesive layer.

Examples of the crosslinking inhibitor against polyfunctional isocyanates include a compound having a hydroxyl group, an amino group, a carboxyl group or a mercapto group. Examples of the compound having hydroxyl group include: alcohols such as methanol and ethanol; glycols such as diethylene glycol, propylene glycol and polyethylene glycol; glycerol monoesters such as oleic acid monoglyceride, caprylic acid monoglyceride and lauric acid monoglyceride; glycerol diesters; silica such as hydrated silicon dioxide and soft silicic anhydride; polyhydric alcohols such as glycerol; and water. Examples of the amino group-containing compound and the carboxyl group-containing compound include an amino acid and a fatty acid, respectively.

Also, the examples of the crosslinking inhibitors against metal alcoholates comprised of titanium or aluminum and metal chelate compounds include various compounds such as water, alcohols, diketones, ketoesters, diesters, fatty acids, acid anhydrides, various esters, hydrogen chloride, and amino acids.

In some cases, a percutaneous penetration enhancer or a buprenorphine to be contained in the buprenorphine percutaneous absorption preparation of the present invention functions as a crosslinking inhibitor. The amount effective to be functioned as a crosslinking inhibitor varies depending on the enhancer or drug and other additives, but the crosslinking inhibition action is strongly generated in most cases when the material is contained in the pressure-sensitive adhesive layer in an amount of 10% by weight or more. When such a material is contained in an amount of 70% by weight or more, it acts not only as a crosslinking inhibitor but also as a plasticizer, so that adhesive property becomes poor, shape-keeping ability disappears and stringiness and adhesive residue occur. Particularly, when a fatty acid monoglyceride such as caprylic acid monoglyceride is blended in the pressure-sensitive adhesive layer, the fatty acid monoglyceride is transferred into a separator to cause poor peeling ability of the pressure-sensitive adhesive layer from the separator.

Thus, according to the present invention, these problems can be resolved by incorporating the crosslinked acrylic copolymer particles in the pressure-sensitive adhesive layer, and release of drugs can be controlled easily by adding various percutaneous penetration enhancers.

EXAMPLES

Examples of the present invention are given below by way of illustration and not by way of limitation. The buprenorphine percutaneous absorption preparation of the present invention was prepared in the following manner to confirm the effects of the present invention. In the following, the term "part" means part by weight, and the term "%" means % by weight.

Inventive Example 1

Preparation of Acrylic Copolymer Solution

Firstly, an acrylic copolymer solution was prepared as follows in order to prepare an acrylic copolymer and crosslinked acrylic copolymer particles, both necessary for forming a pressure-sensitive adhesive layer.

Ninety-five parts of 2-ethylhexyl acrylate, 5 parts of acrylic acid, and 0.2 part by weight of benzoyl peroxide were charged into a four-necked flask, the temperature of the contents was raised to 62 to 65°C in an atmosphere of an inert gas to initiate polymerization reaction, and 125 parts of ethyl acetate was added dropwise to effect the reaction for 8 hours while controlling the reaction temperature, followed by ripening at 75 to 80°C for 2 hours, thereby obtaining an acrylic copolymer solution.

In an atmosphere of an inert gas such as nitrogen gas, 95 parts of 2-ethylhexyl acrylate and 5 parts of acrylic acid were copolymerized in the ordinary manner in ethyl acetate, thereby preparing an acrylic copolymer solution containing an acrylic copolymer.

Preparation of Pressure-sensitive Adhesive Solution Containing Crosslinked Acrylic Copolymer Particles

A trifunctional isocyanate (Coronate HL, manufactured by Nippon Polyurethane Industry Co., Ltd.; the same shall apply hereinafter) was added to the thus obtained acrylic copolymer solution in an amount of 0.13 part per 100 parts of the acrylic copolymer, and the concentration of the acrylic copolymer was adjusted to 25% by adding ethyl acetate. Thereafter, the resulting mixture was put into an airtight container and subjected to heat aging at 60°C for 96 hours to prepare a pressure-sensitive adhesive solution containing crosslinked acrylic copolymer. This solution was found to have a gel percentage of 59% when measured by a method which will be described later (all data of the gel percentage shown in the following were obtained by the same method). The weight ratio of the acrylic copolymer and. crosslinked

acrylic copolymer particles in this pressure-sensitive adhesive solution was found to be 144 parts by weight of the crosslinked acrylic copolymer particles to 100 parts by weight of the acrylic copolymer.

Using a pump for high viscosity use, the thus obtained pressure-sensitive adhesive solution containing crosslinked acrylic copolymer particles was charged into Gorator (manufactured by Nittetsu Mining Co., Ltd.) and pulverized into a particle size of 1 to 2 mm. This was then diluted with ethyl acetate to adjust the concentration of the crosslinked acrylic copolymer particles to 10% and further pulverized using TK Homomixer (manufactured by Tokushu Kika Kogyo K.K.) into a particle size of 1 to 10 μm.

Next, to the thus obtained pressure-sensitive adhesive solution containing cross-linked acrylic copolymer particles were added 10% of buprenorphine hydrochloride, 20% of caprylic acid monoglyceride, 20% of isopropyl myristate and 5% of hydrated silicon dioxide (Carplex, manufactured by Shionogi), and the resulting mixture was uniformly dispersed by stirring. Using a laminated film support prepared from a polyester non-woven fabric (weight basis: 12 g/m^2) and a polyester film (2 μm in thickness), the thus-prepared pressure-sensitive adhesive solution was coated and dried on the non-woven fabric side of the support, in such an amount that the weight of the pressure-sensitive adhesive after drying became 4 mg/cm^2, thereby preparing a pressure-sensitive. adhesive layer. Thereafter, a polyester separator (50 μm in thickness) was pasted on the pressure-sensitive adhesive layer to obtain the percutaneous absorption preparation of Inventive Example 1.

Inventive Example 2

A percutaneous absorption preparation was obtained in the same manner as in Inventive Example 1, except that the trifunctional isocyanate was used in an amount of 0.06 part based on 100 parts by weight of the acrylic copolymer. In this case, the gel percentage of the pressure-sensitive adhesive solution was found to be 41%, and the crosslinked acrylic copolymer particles were contained in an amount of 70 parts to 100 parts of the acrylic copolymer.

Inventive Example 3

A percutaneous absorption preparation was obtained in the same manner as in Inventive Example 1, except that the trifunctional isocyanate was used in an amount of 0.17 part based on 100 parts by weight of the acrylic copolymer. In this case, the gel percentage of the pressure-sensitive adhesive solution was found to be 75%, and the crosslinked acrylic copolymer particles were contained in an amount of 300 parts to 100 parts of the acrylic copolymer.

Comparative Example 1

A three neck flask equipped with a stirrer and a reflux condenser was charged with 600 parts of ion-exchanged water and 0.5 part of polyvinyl alcohol (saponification degree, 78.5 to 81.5%) as a dispersing agent, and the contents were thoroughly mixed by stirring. To this solution was added a monomer mixture consisting of 200 parts of 2-ethylhexyl acrylate, 10 parts of acrylic acid and 0.2 part of benzoyl peroxide. In an atmosphere of an inert gas such as nitrogen gas, the thus prepared solution was stirred at 25°C (300 rpm) for 1 hour and then at 65°C for 4 to 5 hours to effect copolymerization. This was further heated to 80°C and stirred for 2 hours to complete the copolymerization reaction, thereby obtaining a pressure-sensitive adhesive solution containing acrylic copolymer particles which have not been crosslinked. This pressure-sensitive adhesive solution contained 25% of acrylic copolymer particles. The pressure-sensitive adhesive solution was then mixed with 600 parts of methanol to recover the precipitated acrylic copolymer particles. The precipitated acrylic copolymer particles were dispersed in ethyl acetate to obtain a dispersion having a concentration of 10%. The particle size of the acrylic copolymer particles at this stage was found to be 5 to 80 μm. Then, buprenorphine hydrochloride, caprylic acid monoglyceride, isopropyl myristate and hydrated silicon dioxide were added thereto, and a percutaneous absorption preparation was prepared in the same manner as in Inventive Example 1.

Comparative Example 2

A copolymer suspension (Primal N-580 (NF-1), manufactured by Japan Acrylic Chemical Co., Ltd.) obtained in an aminoacetic acid aqueous solution of methacrylic acid and n-butyl acrylate was mixed with the same weight of ethanol to recover the thus precipitated methacrylic acid/n-butyl acrylate copolymer particles. The methacrylic acid/n-butyl acrylate copolymer particles were washed with ethanol and re-dispersed in ethanol to a concentration of 20%. The particle size of the copolymer particles was found to be about 250 to 550 nm. To this solution, were added buprenorphine hydrochloride, caprylic acid monoglyceride, isopropyl myristate and hydrated silicon dioxide, and a percutaneous absorption preparation was prepared in the same manner as in Inventive Example 1.

Comparative Example 3

To the acrylic copolymer solution obtained in Inventive Example 1 were added buprenorphine hydrochloride, caprylic acid monoglyceride, isopropyl myristate and hydrated silicon dioxide in such amounts that their final concentrations in the preparation became equal to those of the percutaneous absorption preparation of Inventive Example 1. Next, the trifunctional isocyanate was added thereto such that the concentration was 0.0585% (corresponds to 0.13 part per 100 parts of the acrylic copolymer). Thus, a pressure-sensitive adhesive solution was prepared. Then, a percutaneous absorption preparation containing buprenorphine hydrochloride, caprylic acid monoglyceride, isopropyl myristate and hydrated silicon dioxide was prepared in the same manner as in Inventive Example 1. Thereafter, the preparation was subjected to heat aging at 70°C for 60 hours to obtain a percutaneous absorption preparation of Comparative Example 3. In this case, the gel percentage of the pressure-sensitive adhesive solution was 25%, and the amount of the crosslinked acrylic copolymer was about 11.25% of the entire pressure-sensitive adhesive.

Comparative Example 4

A percutaneous absorption preparation was prepared in the same manner as in Comparative Example 3, except that the trifunctional isocyanate was not added and the heat aging was not carried out. In this case, the gel percentage of the pressure-sensitive adhesive solution was found to be 18%.

Comparative Example 5

A percutaneous absorption preparation was obtained in the same manner as in Inventive Example 1, except that the trifunctional isocyanate was added in an amount of 0.03 part based on 100 parts by weight of the acrylic copolymer. In this case, the gel percentage of the pressure-sensitive adhesive solution was found to be 29%, and the weight ratio of the cross linked acrylic copolymer particles after pulverization was 40 parts of the crosslinked acrylic copolymer particles to 100 parts of the acrylic copolymer.

Comparative Example 6

A percutaneous absorption preparation was obtained in the same manner as in Inventive Example 1, except that the trifunctional isocyanate was added in an amount of 0.5 part based on 100 parts by weight of the acrylic copolymer. In this case, the gel percentage of the pressure-sensitive adhesive solution was found to be 83%, and the weight ratio of the crosslinked acrylic copolymer particles after pulverization was 500 parts of the crosslinked acrylic copolymer particles to 100 parts of the acrylic copolymer.

Measurement of Gel Percentage

For the measurement of the gel percentage, each of the pressure-sensitive adhesive solutions of acrylic copolymers prepared in the inventive and comparative examples was coated and dried on a backing under ordinary condition for the preparation of a conventional pressure-sensitive adhesive tape, in such an amount that the thickness of the pressure-sensitive adhesive layer after drying became about 40 μm to prepare each sample to be tested by the following method.

A porous film made of tetrafluoroethylene (30 to 100 μm in thickness and 0.1 to 1.0 μm in average pore size) is cut to a piece of 100 mm in width and 200 mm in length, and a sample punched out into a size of 40 cm^2 (corresponds to 60 to 200 mg as the weight of pressure-sensitive adhesive) is adhered to the piece of porous film. Next, a bag of the porous film is made by bending the thus-prepared porous film double in such a manner that the sample is not overlapped and then bending each tip of its three corners twice so that crosslinked acrylic copolymer particles leaked out of the sample do not leak from the bag. The thus prepared bag is soaked for 24 hours in 100 ml of a solvent capable of dissolving an acrylic copolymer such as ethyl acetate. This soaking step is repeated twice. Thereafter, the solvent is evaporated and then each of the following weights is measured to calculate the gel percentage based on the following formula.

$$\text{Gel Percentage (\%)} = [(B - C - D - F)/(A - C - D - E)] \times 100$$

A: weight (g) of the porous film bag (including sample) before soaking
B: weight (g) of the porous film bag (including sample) after soaking
C: weight (g) of the porous film
D: weight (g) of the backing

E: weight (g) of the additive

F: weight (g) of the additive remained in the porous film bag after soaking due to incomplete removal by the solvent

In this connection, when weight C of the porous film and weight D of the backing vary before and after soaking, changes in the weight of the porous film and the backing are respectively measured in advance, and the gel percentage is corrected based on the weight changes. Also, where additives were contained in the pressure-sensitive adhesive solutions (Comparative Examples 3 and 4) from which the samples were prepared, values converted from the blending ratio of additives were used as weights E and F of the additives.

Comparative Tests

Using the percutaneous absorption preparations obtained in Inventive Examples 1 to 3 and Comparative Examples 1 to 6, the following items were tested (measured). The obtained results are shown in Tables 1 and 2.

Table 1

	Adhesive Force (g/12 mm)	Holding Force (min.)	Holding Force/Adhesive Force	Anchor Force (g/12 mm)	Adhesion Test	Coating Test
Inventive Example 1	24	21	0.88	253*2	A	A
Comparative Example 1	15	1.0	0.066	50*2	C*1	C*3
Comparative Example 2	18	1.7	0.094	73*2	B*1	A
Comparative Example 3	21	1.8	0.086	271*1	C*1	A
Comparative Example 4	24	2.1	0.088	294*1	C*1	A

*1: cohesive failure
*2: partial anchor failure
*2: streaked coating and poor appearance

Table 2

	Content of Crosslinked Particles (parts)	Adhesive Force (g/12 mm)	Holding Force (min.)	Holding Force/Adhesive Force	Anchor Force (g/12 mm)	Adhesion Test	Coating Test
Comparative Example 5	40	31	2	0.06	301*2	C*1	A
Inventive Example 2	70	27	9	0.33	271*1	A	A
Inventive Example 1	144	24	21	0.88	253*2	A	A
Inventive Example 3	300	21	23	1.10	101*2	A	A
Comparative Example 6	500	16	≥30*3	---	76*2	B*2	B

*1: anchor failure
*2: partial anchor failure
*3: The sample slipped down and the accurate holding force could not be measured.

Adhesive Force Test

Each sample of the percutaneous absorption preparations cut into a zonal shape of 12 mm in width was laminated on a Bakelite plate, adhered by a pressure of one reciprocation of an 850 g load roller and then peeled off using a Tensilon tensile tester at a rate of 300 mm/min to its 180 degree direction under conditions of 23°C and 60% R.H. to measure peeling strength (g).

Holding Powder Test

A 20 mm in length of one tip of each sample of the percutaneous absorption preparations cut into a size of 10 mm in width and 50 mm in length was laminated on a tip of a Bakelite plate and adhered by a pressure of one reciprocation of an 850 g load roller, and 150 g of load was applied to the other tip of the sample and then stored at 40°C. The time (minute) until each sample was dropped due to generation of cohesive failure was measured.

Anchor Force Test

The backing side of a placebo tape cut into a size of 13 mm in width and 100 mm in length (a tape prepared from each of percutaneous absorption preparations obtained in the same manner as in the respective Inventive and Comparative Examples except that the drugs and additives were not added) was fixed on a Bakelite plate of 25 x 100 mm in size using a pressure-sensitive adhesive double coated tape. The pressure-sensitive adhesive layer side of each sample of the percutaneous absorption preparations cut into a size of 12 mm in width and 70 mm in length was adhered to the pressure-sensitive adhesive layer side of the placebo tape using an 850 g load roller and then the sample was immediately peeled off using a Tensilon tensile tester at a rate of 300 mm/min in the 90 degree direction under conditions of 23°C and 60% R.H. to measure load stress (g).

Judgement of Anchor Force

In the measurement, the anchor force to the backing was evaluated as a load stress at the time of clean peeling between the backing and pressure-sensitive adhesive layer of each of the percutaneous absorption preparations prepared in Inventive and Comparative Examples. A case was judged as cohesive failure when a failure phenomenon of the pressure-sensitive adhesive layer, such as stringiness, was observed during the measurement due to residual pressure-sensitive adhesive layer on the backing. Also, an intermediate case of the aforementioned phenomenon in which

the pressure-sensitive adhesive layer was found partially remaining on the backing was judged as partial anchor failure. In addition, a case in which the pressure-sensitive adhesive layer of each of the percutaneous absorption preparations prepared in Inventive and Comparative Examples and the pressure-sensitive adhesive layer of the placebo tape were cleanly peeled off from each other was judged as interface peeling. A case where a pressure-sensitive adhesive layer is peeled off from the support was judged as anchor failure. It is considered that the percutaneous absorption preparations prepared in Inventive and Comparative Examples have sufficient anchor force and aggregation property when the interface peeling or placebo tape anchor failure is observed.

Human Skin Adhesion Test

Each sample of the percutaneous absorption preparations cut into a size of 30 mm in width and 50 mm in length was adhered to an inside part of a forearm of a healthy volunteer. After 1 hour of the adhesion, the sample was peeled off to observe its anchor failure condition. The evaluation was conducted based on the following criteria.

A : No generation of anchor failure or adhesive residue.
B : Slight generation of anchor failure or cohesive failure on the edge part and residue of the pressure-sensitive adhesive on the skin.
C : Generation of anchor failure or cohesive failure on the entire surface and residue of the pressure-sensitive adhesive on the skin.

Coating Property and Appearance Test

Coating property at the time of coating and appearance of the prepared percutaneous absorption preparations were evaluated based on the following criteria.

A : Smooth coat surface and no abnormal appearance.
B : Slight streaked coating and irregularity on the coat surface, but no particular problems in appearance.
C : Extreme streaked coating and irregularity on the coat surface and not suitable as a preparation due to rough appearance.

Test Results

As can be seen from the results shown in Table 1, the percutaneous absorption preparation of Inventive Example 1 showed almost the same adhesive force as those of Comparative Examples 1 to 4, though the adhesive force was weak wholly due to the influence of caprylic acid monoglyceride. Also, it showed excellent result in the holding power test, and its result of the human skin adhesion test was practical because of no generation of adhesive residue. In the anchor force test, all of the samples showed markedly strong anchor force and cannot therefore be measured as complete anchor failure because of the use of a support made of a laminate film of a polyester non-woven fabric and a polyester film. However, the large quantity of stringiness observed in the preparations of Comparative Examples 3 and 4 due to their cohesive failure was not found in the case of the percutaneous absorption preparation of Inventive Example 1 which also showed about 3.5 times higher anchor force than that of the preparation of Comparative Example 2, so that the inventive preparation was confirmed to be an excellent percutaneous absorption preparation.

The phenomenon of a large quantity of stringiness suggests that caprylic acid monoglyceride and hydrated silicon dioxide acted to inhibit the cross linking of the acrylic copolymers in the compositions of the percutaneous absorption preparations of Comparative Examples 3 and 4. Particularly, the percutaneous absorption preparation of Comparative Example 2, in which a granular pressure-sensitive adhesive was used, exhibited excellent coating property as compared with that of Comparative Example 1, but exhibited adhesive residue generated on the edge part in the human skin adhesion test, which made the preparation insufficient in practical use.

Table 2 shows the comparison of percutaneous absorption preparations having different amounts of crosslinked acrylic copolymer particles. The term "crosslinked particle content" used in Table 2 means the content (parts by weight) per 100 parts by weight of acrylic copolymer. As seen from the results shown in Table 2, the percutaneous absorption preparations of Inventive Examples 1 to 3 were excellent in cohesive force because of the high holding force, as compared with that of Comparative Example 5, and were excellent in adhesive force, anchor force and coating property, as compared with that of Comparative Example 6, and exhibited the excellent results in terms of their stringiness and anchor force in the human skin adhesion test. Thus, it was confirmed that the percutaneous absorption preparations of Inventive Examples 1 to 3 were practically useful.

Fig. 1 shows the relationship between the content ratio of crosslinked acrylic copolymer particles and the physical properties of the percutaneous absorption preparations of Inventive Examples 1 to 3 and Comparative Examples 4 and

6. In the drawing, open circles (- ○ -) indicate adhesive force, saltires (- X -) indicate holding force and open triangles (- △ -) indicate the ratio of holding force to adhesive force (holding force/adhesive force). It can be seen from this drawing that the preparation having well-balanced holding force/adhesive force value of 0.5 or more contains 100 parts by weight or more of crosslinked acrylic copolymer particles per 100 parts by weight of the acrylic copolymer.

Fig. 2 shows the relationship between the added amount of a crosslinking agent and the gel percentage of a pressure-sensitive adhesive solution containing cross linked acrylic copolymer particles, which indicates that the amount of the added crosslinking agent exceeding 0.17 part by weight per 100 parts by weight of the acrylic copolymer before crosslinking (corresponds to 300 parts by weight of the crosslinked acrylic copolymer particles) is not effective in proportionally improving the formation ratio of the crosslinked acrylic copolymer particles.

From these results, it can be seen that a preparation having a holding force/adhesive force value of 0.5 or more, preferably close to 1 shows well-balanced relation between the adhesive force and cohesive force and therefore is an excellent adhesion type percutaneous absorption preparation which does not practically cause stringiness and adhesive residue. From the results of the human skin adhesion test, it can be seen that the crosslinked acrylic copolymer particles should be 70 parts by weight or more as the practical level, but preferably 400 parts by weight or less from the point of view of coating property.

As described above, the percutaneous absorption preparations obtained in Inventive Examples 1 to 3 are practically markedly excellent percutaneous absorption preparations which show well-balanced relation between the adhesive force and cohesive force, have a soft touch because of the incorporation of a percutaneous penetration enhancer, namely have less irritation to the skin, and exert high pharmacological activities due to its absorption enhancing effect.

The pressure-sensitive adhesive layer of the buprenorphine percutaneous absorption preparation according to the present invention comprises an acrylic polymer containing therein crosslinked acrylic copolymer particles prepared by crosslinking and pulverizing an acrylic copolymer, and the cohesive force of the pressure-sensitive adhesive layer can be increased and a percutaneous absorption preparation being excellent in coating property and appearance can be provided.

Furthermore, the percutaneous absorption preparation is also excellent in anchor force, it can exhibit reduced generation of stringiness and adhesive residue.

In the case where a buprenorphine or a percutaneous penetration enhancer has crosslinking inhibition action, the preparation according to the present invention is especially effective, and the pressure-sensitive adhesive characteristics can be controlled without being affected by cross linking inhibitors. For example, the present invention is suitable in the case where a fatty acid monoglyceride is added as a percutaneous penetration enhancer.

While the invention has been described in detail with reference to specific embodiments, it will be apparent to one skilled in the art that various changes and modifications can be made to the invention without departing from its spirit and scope.

Claims

1. A buprenorphine percutaneous absorption preparation comprising a backing having formed on one side thereof a pressure-sensitive adhesive layer containing at least one of buprenorphine and a salt thereof, wherein the pressure-sensitive adhesive layer contains an acrylic copolymer and crosslinked acrylic copolymer particles such that the crosslinked acrylic copolymer particles are present in an amount of 70 to 400 parts by weight per 100 parts by weight of the acrylic copolymer.

2. The buprenorphine percutaneous absorption preparation of claim 1, wherein the crosslinked acrylic copolymer particles are those prepared by subjecting an acrylic copolymer to crosslinking and pulverisation.

3. The buprenorphine percutaneous absorption preparation of claim 1, wherein the pressure-sensitive adhesive layer further contains a percutaneous penetration enhancer.

4. The buprenorphine percutaneous absorption preparation of claim 1, wherein the pressure-sensitive adhesive layer further contains a fatty acid monoglyceride as a percutaneous penetration enhancer.

5. The buprenorphine percutaneous absorption preparation of claim 2, wherein the pressure-sensitive adhesive layer further contains a percutaneous penetration enhancer.

6. The buprenorphine percutaneous absorption preparation of claim 2, wherein the pressure-sensitive adhesive layer further contains a fatty acid monoglyceride as a percutaneous penetration enhancer.

7. A method for producing a buprenorphine percutaneous absorption preparation comprising a backing having

formed on one side thereof a pressure-sensitive adhesive layer containing at least one of buprenorphine and a salt thereof, which comprises:

adding a crosslinking agent to a solution of an acrylic copolymer to effect crosslinking,
subjecting the resulting solution to pulverization to prepare a pressure-sensitive adhesive solution containing an acrylic copolyner and crosslinked acrylic copolymer particles,
adding at least one of buprenorphine and a salt thereof and optionally a percutaneous penetration enhancer and other additives to the pressure-sensitive adhesive solution, and
coating the backing with the resulting pressure-sensitive adhesive solution to form a pressure-sensitive adhesive layer.

Fig. 1

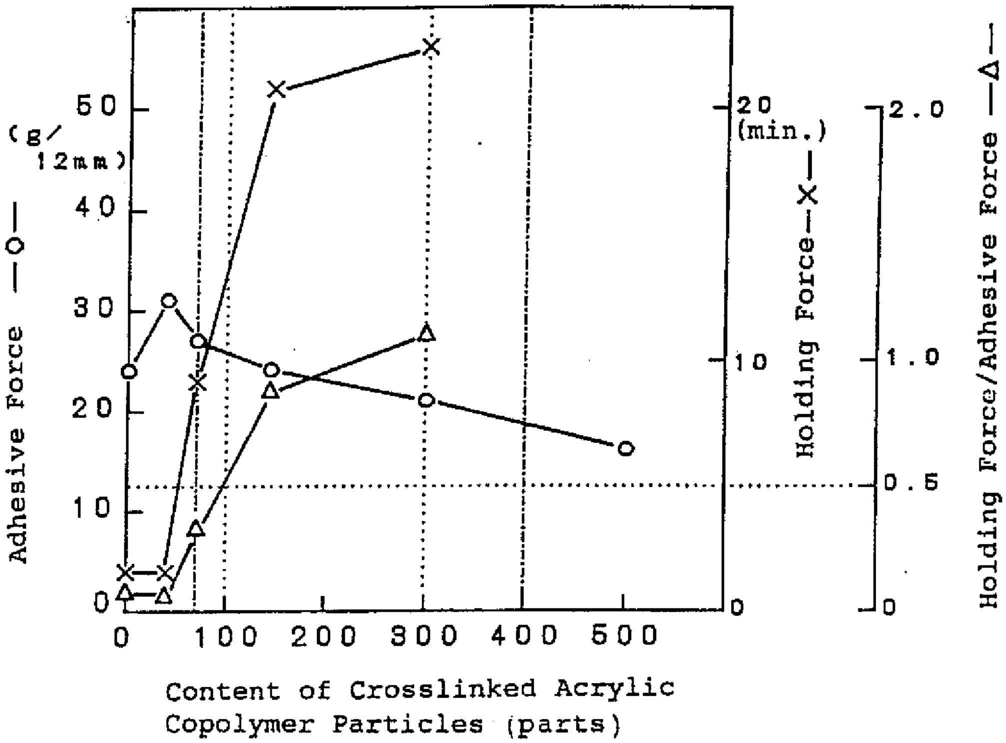
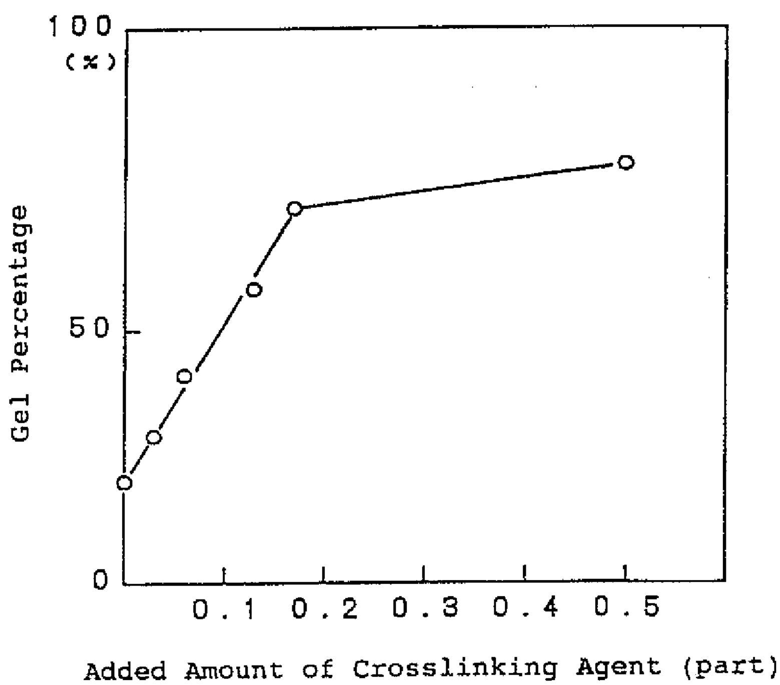

50
(g/12mm)
40
30
20
10
0
Adhesive Force —O—
20 (min.)
10
0
Holding Force—X—
2.0
1.0
0.5
0
Holding Force/Adhesive Force —Δ—
0
100
200
300
400
500
Content of Crosslinked Acrylic Copolymer Particles (parts)

Fig. 2


100 (%)
50
0
Gel Percentage
0.1
0.2
0.3
0.4
0.5
Added Amount of Crosslinking Agent (part)